Evidence-based Practice Center Systematic Review Protocol

Project Title: Prevention of Contrast Media Induced Nephropathy

I. Background and Objectives for the Systematic Review

Contrast induced nephropathy (CIN) is defined as impairment of renal function, an increase in serum creatinine levels by more than 25 percent or 0.5 mg/dL, occurring within 3 days after intravascular administration of contrast media in the absence of an alternative etiology. If renal function returns to normal, it usually does so within 7 to 10 days after contrast medium administration.[1] However, sometimes CIN progresses to acute kidney injury (AKI), which can be defined as a two-fold increase in the serum creatinine or a 50 percent decreased in glomerular filtration rate (GFR) or urine output less than 0.5 mL/kg per hour for 12 hours. Various types of imaging studies or procedures use intravascular contrast media including, intravenous (IV) pyelograms, brain or head and neck or body or coronary computed tomograms (CT), cerebral or cardiac or peripheral vascular angiograms, and radiologic therapeutic procedures. Contrast is injected IV for computed tomography and intra-arteriorly (IA) for angiograms and related interventional procedures. More than 62 million CT studies were performed in the United States in 2006 and the use of CT has tripled between 1996 and 2010, from 52 studies per 1000 patients to 149 studies per 1000 patients.[2]

The reported incidence of CIN varies, with estimates as high as 12%.[3] Most of the estimates have been derived from invasive angiographic studies using IA contrast media, that may have a higher risk of CIN than imaging studies using IV contrast media. One problem in determining the precise incidence of CIN is that it often is difficult to distinguish the effects of contrast media from the effects of physiologic confounders that could elevate the serum creatinine in patients undergoing these radiologic studies.[4, 5]

Numerous strategies to prevent CIN have been used, including: oral hydration; volume expansion with sodium chloride or bicarbonate or a combination of both; administration of N-acetylcysteine (NAC); withdrawal of metformin, ACE (angiotensin-converting-enzyme) inhibitors, angiotensin II receptor blockers, or non-steroidal anti-inflammatory drugs; hemofiltration or hemodialysis; use of low osmolar, non-ionic, contrast media; and reducing the volume of contrast media administered.

Although evidence on the topic has been cited in various clinical practice guidelines[6-9] (for radiologists, cardiologists, and nephrologists) and previous systemic reviews,[3, 10-12] many uncertainties about the topic remain. Most of the primary studies focus on specific subsets of patients that had imaging studies or procedures with contrast media and therefore the generalizability of the studies is unclear. Uncertainty also exists regarding several issues, including: a) the incidence and precise etiology of CIN in patients who receive IV versus IA contrast media[5]; b) the efficacy of oral hydration versus intravascular volume expansion in preventing CIN[13, 14];c) the optimal timing (pre- versus post-contrast administration or both), duration, and type of intravascular fluids used to prevent CIN[15]; and d) the comparative risks and benefits of low versus iso-osmolar contrast media. The purpose of this report is to either resolve these uncertainties, or point

out that they still exist and more research is needed.

Ionic, high osmolar (HOCM) contrast media (five to eight times the osmolality of plasma, or greater than 1500 mOsm/kg) are no longer used due to their nephrotoxicity. LOCM and IOCM are now used in clinical practice instead. Non-ionic monomer LOCM, such as iopamidol, iohexol, and iomeprol, have two- to three times the osmolarity of plasma (600 to 850 mOsm/kg). IOCM, such as iodixanol, which are being used increasingly, have the same osmolality (290 mOsm/kg) as blood, plasma, and cerebrospinal fluid. The cost of IOCM is generally higher than LOCM. LOCM are less likely to cause CIN than the old HOCM.[16] However, there are conflicting results from studies that have compared CIN risk of IOCM versus LOCM.[17-19] It is unclear whether the additional cost of IOCM is accompanied by a reduced risk of CIN. Also, it is not entirely clear how image quality and the risk of CIN differ between LOCM and IOCM.[17-19]

The route of administration of contrast may play a significant role in determining the risk of CIN. The IA route may confer more risk than the IV use,[5, 20, 21] but that risk may be confounded by the pre-existing risk profile of patients undergoing an IA contrast media procedure versus an IV contrast media imaging study. Patients who undergo an IA contrast media procedure such as a cerebral or coronary or peripheral angiogram or an interventional procedure, are more likely to have pre-existing cardiac, vascular and renal risk factors, which may inherently predispose them to elevation in serum creatinine when IA contrast is administered. Patients who undergo an IV contrast media imaging study on an outpatient basis are likely to have less co-morbidity and fewer pre-existing risk factors for elevation of serum creatinine.

The two most recent large primary studies produced discrepant results concerning the impact of contrast media on kidney function in patients who underwent imaging tests with IV contrast media and those who underwent similar tests without IV contrast media.[5, 21] A recent systemic review included only studies with patients undergoing IV contrast media and control groups without IV contrast media, and showed that the risk of AKI was similar in the two groups, regardless of IV contrast medium type, diagnostic criteria used for AKI, or if the patient had diabetes mellitus or preexisting renal insufficiency.[20] That systemic review added to the controversy about whether IV contrast media contributes to AKI in patients undergoing imaging studies. This emphasizes the need for a comprehensive evidence-based synthesis of risks for patients undergoing IV contrast media imaging studies such as computed tomography (CT) versus IA contrast media procedures such as a cardiac angiogram, cerebral angiogram, or peripheral vascular angiogram. These are two distinct subsets of populations that must be considered in assessing the causal association between administration of contrast media and AKI, as well as in determining the effectiveness of interventions to prevent CIN.

The threshold volume or dose of contrast to induce CIN is also controversial, and strongly depends on the risk profile of the patients and the type of study performed. Recent publications have questioned the role of N- acetylcysteine (NAC),[8] withdrawal of nephrotoxic drugs,[22] and hemodialysis or hemofiltration in preventing CIN. The 2007 American College of Radiology practice guideline focuses on how to administer contrast and which patients are most likely to benefit from LOCM, rather than the evidence for or against different preventive measures.{http://www.acr.org/Quality-Safety/Standards-Guidelines} A guideline on the prevention of CIN was published in 2007 by the

Canadian Association of Radiologists.[6] These guidelines were published following what is described in the guideline as an 'in-depth literature search with critical review'; however, no further details are included about the methods. Guidelines were also issued by the CIN Consensus Working Panel in 2006, an international multidisciplinary group convened to address challenges related to CIN, but these guidelines were based on an evidence review through 2005.[3] In general, these guidelines overlap and agree on the use of prevention measures, including adequate hydration, minimizing contrast media exposure, and using low or iso-osmolar contrast media (IOCM) in patients with chronic kidney disease. The quality of method of synthesis is variable among these guidelines and many of these guidelines are consensus opinion of clinical experts.

We briefly reviewed the seven meta-analyses published within the last 12 months on CIN and summarized their findings (Table 1) related to our Key Questions.[20, 23-28] These meta-analyses focused primarily on the incidence of CIN by route of administration of contrast media and various prevention methods. Their results are varied and conflicting, likely due to the varied inclusion criteria. Based on the increasing use of contrast media, the increasing prevalence of populations vulnerable to CIN (i.e., people having chronic kidney disease, diabetes mellitus, or hypertension, and the elderly), increasing use of radiologic and cardiologic studies, and controversial and discrepant results from various prior meta analyses, a comprehensive systematic review of this topic will be extremely valuable to clinicians who wish to minimize the risk of CIN in patients undergoing imaging studies.

II. The Key Questions

Preliminary Key Questions (KQs)

KQ 1:	In patients undergoing imaging studies requiring **intravenous** contrast media, what is the comparative effectiveness of interventions to prevent contrast induced nephropathy (CIN), for the outcomes of incidence of CIN, chronic kidney disease (CKD), end stage renal disease (ESRD), mortality, and other adverse events? a. How does the comparative effectiveness of prevention measures vary by patient characteristics (known risk factors such as age, comorbidity, glomerular filtration rate (GFR), or creatinine level)? b. How does the comparative effectiveness of prevention measures vary according to the type of contrast medium used? c. How does the comparative effectiveness of prevention measures vary by characteristics of the interventions (e.g., dose, duration, and timing)?
KQ 2:	In patients undergoing imaging studies requiring **intra-arterial** contrast media, what is the comparative effectiveness of interventions to prevent contrast induced nephropathy, for the outcomes of incidence of CIN, CKD, ESRD, mortality, and other adverse events? a. How does the comparative effectiveness of prevention measures vary by patient characteristics (known risk factors such as age, comorbidity, GFR, or creatinine level)? b. How does the comparative effectiveness of prevention measures vary according to the type of contrast medium used? c. How does the comparative effectiveness of prevention measures vary by characteristics of the interventions (e.g., dose, duration, and timing)?
KQ 3:	What are the comparative benefits and harms of different contrast media in patients receiving imaging studies requiring **intravenous** administration?

	a. How do benefits or harms of contrast media differ by patient characteristics (known risk factors such as age, comorbidity, GFR, or creatinine clearance)? How do benefits or harms differ by the dose of contrast medium (i.e., by volume of dose and number of doses)? b. How do benefits or harms of contrast media differ according to the type of preventive strategy used?
KQ 4:	What are the comparative benefits and harms of different contrast media in patients receiving imaging studies requiring **intra-arterial** administration? a. How do benefits or harms of contrast media differ by patient characteristics (known risk factors such as age, comorbidity, GFR, or creatinine level)? How do benefits or harms differ by the dose of contrast medium (i.e., by volume of dose and number of doses)? b. How do benefits or harms of contrast media differ according to the type of preventive strategy used?

No changes have been made to the Key Questions since the questions were posted for public comment. Public commenters suggested that we consider addressing the value of stopping medications known to have adverse effects on kidney function, such as ACE inhibitors, and angiotensin II receptor blockers, and the potential value of statins; we have added these to the list of interventions. Additionally, they recommended that we include the following guideline in the review: "Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and interventions,"[29] as well as other documents while developing the comparative effectiveness review.[30, 31] The commenters cited a specific article for inclusion under Key Question 1b,[32] and Key Question 1c.[33, 34] We will consider including them in the review as long as they meet the inclusion criteria defined for this comparative effectiveness review.

PICOTS Criteria

The PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Setting) framework for the review includes the following items.

Population(s)

All Key Questions

- All patients (including adults and children) undergoing procedures requiring the administration of contrast media.
- High or moderate risk patients (as defined by clinical or demographic risk factors such as age, cardiovascular and other comorbidities, creatinine level etc) versus low risk or normal patients
- Patients using contrast media for multiple imaging studies

Interventions

Key Question 1 and Key Question 2(see Table 2)

- IV Volume expansion with sodium chloride (NaCl)
- IV Volume expansion with sodium bicarbonate
- IV Volume expansion with NaCl and sodium bicarbonate
- IV or oral N-acetylcysteine (high dose)
- IV fluids without pharmacologic agents

- Oral fluids
- IV fluids with pharmacologic agents
- Oral Statins (**Key Question** 2 only)
- IV Dopamine
- IV Fluids matched to urine output
- Discontinuation of metformin because of concern about inducing lactic acidosis
- Discontinuation of medications that could have adverse effects on kidney function (e.g., ACE inhibitors, angiotensin II receptor blockers, diuretics, and non-steroidal anti-inflammatory drugs)
- Renal replacement therapy (RRT) (e.g., hemodialysis or hemofiltration)

Key Question 3 and Key Question 4 (see Table 3)

- IOCM (including dose/volume and number of doses)
- LOCM (including dose/volume and number of doses)

Comparators

Key Question 1 and Key Question 2 (see Table 2)

- Usual care versus any of the interventions listed above
- Volume expansion with NaCl versus volume expansion with sodium bicarbonate
- Volume expansion with NaCl versus volume expansion with NaCl and sodium bicarbonate
- Volume expansion with sodium bicarbonate versus volume expansion with NaCl and sodium bicarbonate
- N-acetylcysteine (high dose) versus N-acetylcysteine (low dose)
- Timing and duration of above

  Note: These are the important comparisons that are most likely to have sufficient evidence to merit inclusion in a systematic review. Other comparisons may be identified after a more thorough literature search, but they are unlikely to be relevant to modern clinical practice or have enough evidence to merit inclusion in the review.

Key Question 3 and Key Question 4 (see Table 3)

- IOCM versus LOCM
- LOCM versus LOCM
- IOCM (by dose/volume) versus IOCM (by dose/volume)
- IOCM (by dose/volume) versus LOCM (by dose/volume)
- LOCM (by dose/volume) versus LOCM (by dose/volume)
- IOCM (number of doses) versus IOCM (number of doses)
- IOCM (number of doses) versus LOCM (number of doses)
- LOCM (number of doses) versus LOCM (number of doses)
- Timing and duration of contrast media

Outcomes

Key Question 1 and Key Question 2

Short-term (< 7 days):

a) Harms of prevention interventions

- Imaging delay
- Need for additional imaging

- Fluid overload
- Heart failure

b) Renal function measures
- Development of CIN as defined by change in creatinine or change in GFR

c) Renal disease-specific outcomes
- Need for RRT (dialysis or hemofiltration)

d) Other clinical outcomes
- Mortality (in hospital or within 7 days)
- Cardiac outcomes

e) Prolonged hospital stay

Long-term (> 7 days):

a) Renal function measures
- Development of CKD, including end stage renal disease (ESRD)
- Rate of conversion to CKD at 3 and 6 months
- Chronic change in kidney function

b) Renal disease-specific outcomes
- Need for RRT (dialysis, hemofiltration, or kidney transplant)

c) Other clinical outcomes
- Cardiac outcomes
- Mortality in hospital or at 3 or 6 months

Key Question 3 and Key Question 4

Short-term:

a) Renal function measures
- Development of CIN as defined by change in creatinine or change in GFR

b) Renal disease-specific outcomes
- Need for RRT (dialysis or hemofiltration)

c) Other clinical outcomes
- Mortality (in hospital or within 7 days)
- Cardiac outcomes
- Anaphylaxis

d) Prolonged hospital stay

e) Benefits of radiographic imaging with contrast media
- Intermediate outcomes
  - Image quality (resolution, contrast)
  - Diagnostic performance (test characteristics)
- Clinical benefits of image quality
  - Improved morbidity
  - Improved mortality
  - Minimization of other imaging tests and procedures

Long-term:

a) Renal function measures
- Development of CKD, including ESRD
- Rate of conversion to CKD at 3 and 6 months
- Chronic change in kidney function

b) Renal disease-specific outcomes
- Need for RRT (dialysis, hemofiltration, or kidney transplant)

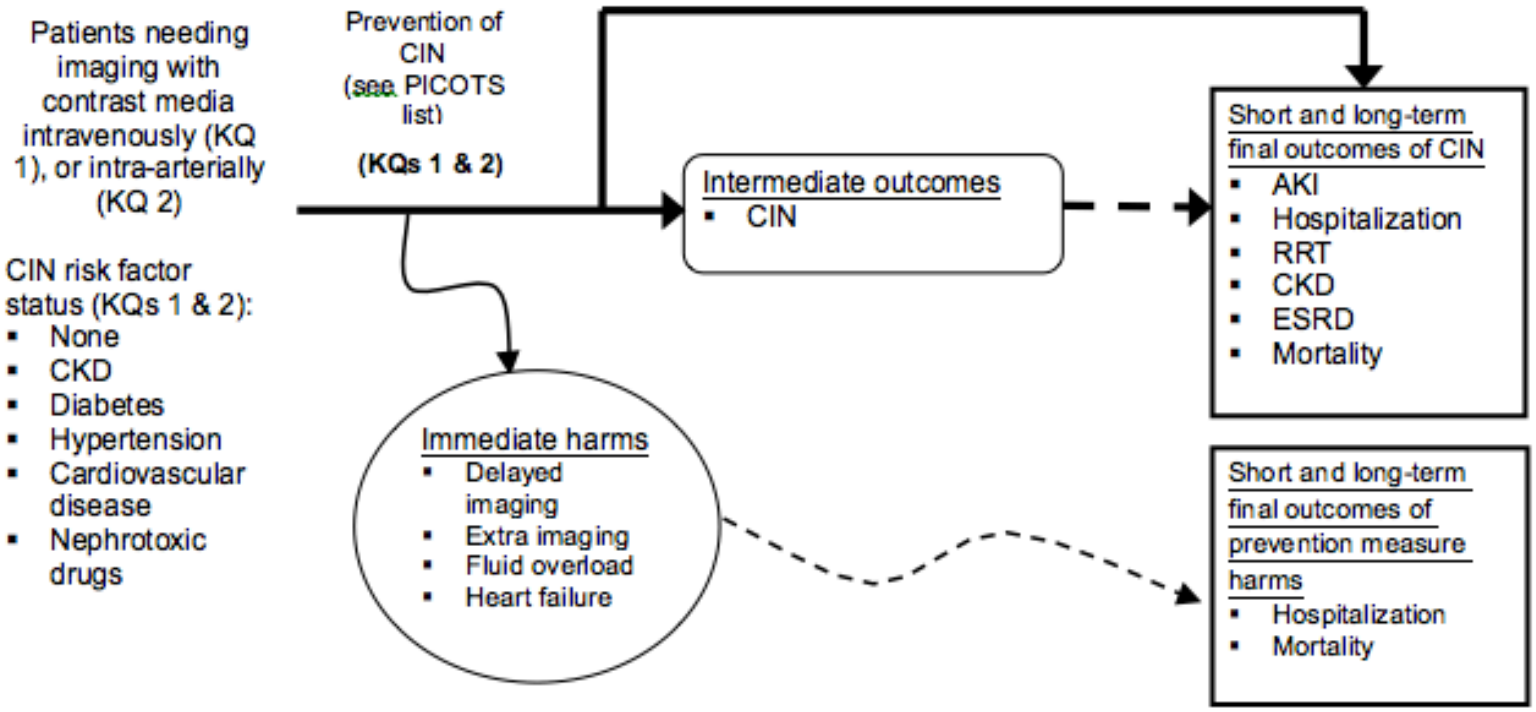
c) Other clinical outcomes
- Cardiac outcomes
- Mortality in hospital or at 3 or 6 months
- Long-term clinical benefits of image quality
  - Improved morbidity
  - Improved mortality
  - Minimization of other imaging tests

Timing
- Short-term: inpatient or within 7 days of procedure
- Long-term: at least 30 days after procedure. For observational studies, the followup should be followed for at least 2 years.

Setting
- **Key Question** 1 through **Key Question** 4
  - Inpatient and outpatient populations

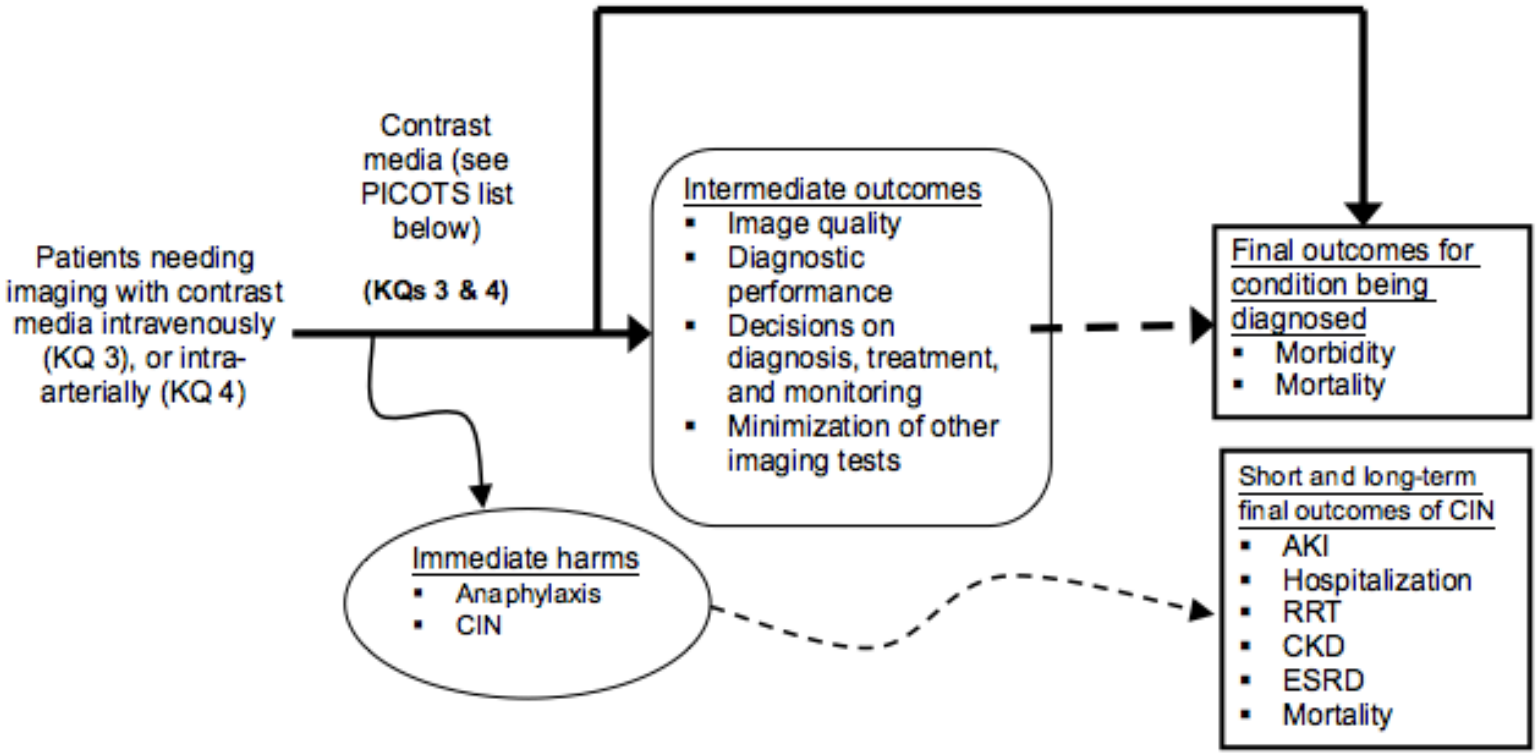
III. Analytic Framework

Figure 1a. Analytic Framework: Examining Interventions to Prevent Contrast Induced Nephropathy, Key Questions 1 and 2.



AKI=acute kidney injury; CIN=contrast induces nephropathy; CKD=chronic kidney disease; ESRD=end stage renal disease; KQ=Key question; RRT=renal replacement therapy

Figure 1b. Analytic Framework: Comparing Benefits and Harms of Different Contrast Media, Key Questions 3 and 4.



AKI=acute kidney injury; CIN=contrast induces nephropathy; CKD=chronic kidney disease; ESRD=end stage renal disease; KQ=Key question; RRT=renal replacement therapy

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review –We will follow the above defined PICOTS framework in developing the criteria for inclusion of studies in the review. For all **Key Question** s, we will include studies of patients of all ages having low, moderate, or high risk of developing CIN. Patient risk will be recorded in this review as it is reported in the literature. We anticipate there would be heterogeneity in the pretest risk assessment or stratification and would report on the heterogeneity as it is defined by various studies. Serum creatinine or GFR must be assessed prior to and after (up to 72 hours) contrast media injection. All included studies will require that the intervention group receive either IOCM or LOCM via IV or IA injection. Studies must include at least one of the outcomes listed in the PICOTS framework. We will include randomized controlled trials and prospective cohort studies for all key questions. We will include observational studies when there are no RCTs available in the literature. We are not limiting the search to specific dates or languages. Studies that do not meet the above detailed inclusion criteria will be excluded.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Question s – A comprehensive search strategy has been developed for use in PubMed, EMBASE, and the Cochrane Library (see Appendix A). These data bases were selected based on internal expert opinion that they would identify most of the relevant literature on this topic. Start dates of the searches will not be limited. Searches will be updated when the draft report is submitted for peer review. We will hand search the references of relevant systematic reviews to identify additional relevant articles.

We will search the following grey literature sources to identify evidence that may not appear in the peer reviewed literature, or is on-going: Clinical Trials.gov, and SCOPUS. We will search the FDA mini-sentinel site (www.mini-sentinel.org/assessments/default.aspx) for data available on FDA approved drugs or intravascular contrast media. Additionally, we will explore the FDA AERS database for reported adverse events attributed to contrast media or drugs used to prevent CIN. Searching of the AERS database will be facilitated by the Scientific Resource Center. Additionally we will look for relevant information in the Scientific Information Packages (SIP) that will be requested from the manufacturers of products used to prevent CIN. The purpose of the grey literature search is to identify additional sources of data that will be included in the final comparative effectiveness review as well as to identify publication bias.

Additional sources of scientific information will include abstracts from the following professional society meetings: The Trans-catheter Cardiovascular Therapeutics conference, Radiological Society of North America (past and upcoming meetings), and Society of Abdominal Radiology (past and upcoming meetings). We will search the following databases for summarized documents related to this comparative effectiveness review: Health Technology Assessment International, Center for Reviews and Dissemination, The Prognosis Consortium, and Swedish Coronary Angiography and Angioplasty Register.

Due to the projected volume of literature, we will screen titles first, then screen abstracts for relevance to the key questions based on the above inclusion/exclusion criteria. Titles and abstracts will be screened independently by two reviewers. Inclusion at the title screening level will be liberal; if a single reviewer believes an article may contain relevant information based on title, the article will move to the next level (abstract) for further screening. Abstracts require that both reviewers agree on either inclusion or exclusion. Disagreements that cannot be resolved by the two reviewers will be resolved by the internal experts.

Full text articles included at the abstract level will be reviewed independently by two reviewers and require agreement between the reviewer for either inclusion or exclusion. Disagreements that cannot be resolved by the two reviewers will be resolved by a third expert member of the team.

At random intervals during screening, quality checks by senior team members will occur to ensure that screening is consistent with inclusion/exclusion criteria.

We will evaluate existing systematic reviews on the topic to determine the extent to which they address our specific Key Questions. If a high quality (based on the AMSTAR)[35] systematic review addresses one of our specific Key Questions, we will attempt to incorporate that information into our review. Our ability to incorporate a previous review into our review will depend on whether the methods of the review are consistent with our protocol. At a minimum, we will check to make sure that studies included in previous reviews of the topic are taken into consideration in our review.

C. Data Abstraction and Data Management – We will use Distiller SR (Evidence Partners, Ottawa, Canada) to manage the screening process. Distiller SR is a web-based data management program that manages all levels of the review process. All applicable articles identified by the search process are uploaded to the system.

Data from applicable articles will be abstracted directly to the Systematic Review Data Repository™ (SRDR), a web-based data repository. This source serves as both an archive and a data abstraction tool. Data will be exported from SRDR into a project-specific database to serve as archived or backup copies and to create detailed evidence and summary tables.

We will use a systematic approach to extract the data to minimize the risk of bias or errors in this process. We will create standardized forms for data abstraction, which will be pilot tested. By creating standardized forms for data extraction, we will maximize consistency in identifying pertinent data available for synthesis. Each article will undergo double review by study investigators for data abstraction. The second reviewer will confirm the first reviewer's abstraction for completeness and accuracy. A third reviewer will randomly audit a sample assessed by the first two reviewers to ensure consistency in the data abstraction. Articles referring to the same study will be abstracted on a single review form if reporting on the same data, or on separate forms if necessary with clear information provided that the results should be interpreted as from the same study. Reviewers will not be masked to the articles' authors, institution, or journal.

For all articles, reviewers will extract information on general study characteristics (e.g., study design, study period, and followup), pre test (IV contrast administration) risk stratification (including co morbidities), study participants (e.g., age, sex, race/ethnicity), eligibility criteria as defined in the PICOTS, interventions (e.g., contrast used, dose,

duration), outcome measures and the method of ascertainment, and the results for each outcome including the measure of variability.

D. Assessment of Methodological Risk of Bias of Individual Studies – The assessment of risk of bias will be conducted independently and in duplicate based on the Cochrane Risk of Bias tool for randomized studies, and the Newcastle-Ottawa Scale for observational studies.[36,37] We will supplement these tools with additional assessment questions, such as use of appropriate analysis, based on recommendations in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[38] We will include observational studies if they have an appropriate comparison group relevant to one of the key questions and adequate long-term follow up. We will exclude studies if they do not meet a minimal standard (described below) for accounting for potential confounders including a defined control group, adjustments for differences between groups in baseline renal function/status, risk factors, age, and sex. We will not include observational studies with high osmolar contrast media, and we will not consider observational studies with less than 100 participants or less than 2 years of follow up. We will compare the included observational studies to any RCTs. If there is a discrepancy between the observational studies and the RCTs, the overall strength of evidence will be downgraded based on the inconsistency of the evidence. However, greater weight will be given to studies of higher quality (i.e., RCTs). We will follow the EPC methods guide on grading the strength of evidence by looking at the strength of evidence for any RCTs and separately considering the strength of evidence for observational studies. If we conclude that the findings do differ in material ways between the RCTs and the observational studies, we will give greater weight to the RCTs (the lower risk-of-bias studies) and will consider limiting the main analysis to these studies. The higher risk-of-bias studies could be considered in a sensitivity analysis. [37].

E. Data Synthesis – We will review all primary studies, as defined by our inclusion criteria and key questions, as well as recent meta-analyses. If the quality of methods, risk of bias assessment and analyses are adequate in the meta-analyses,[35] then we will add the more recent studies to studies included in the previous analyses and update the meta-analyses. Otherwise, we will perform a de novo meta-analysis including all studies which meet our inclusion criteria.

We will include observational studies if they include more than 100 participants, have at least two years of followup. Randomized controlled trials have been recognized as providing the highest standard of evidence and claims have been made that observational studies may overestimate treatment benefits. Randomized controlled trials (RCTs) constitute the gold standard for the generation of evidence-based medicine, but may not always be feasible. We will not include studies in this review that combine intravenous and intra arterial administration as a comparison group. If we do include data from both RCTs and observational studies, it will not be pooled.[39-41]

We will attempt to address heterogeneity using subgroup analysis and meta-regression if there is sufficient number of studies, or we will describe the heterogeneity qualitatively. We will combine clinically or methodologically diverse studies if the effect sizes are similar, particularly when the power to detect variation is large. In this situation, we will describe the differences among the studies and population characteristics, as well as the rationale for combining them in light of these differences.

From our initial screening of primary studies that was performed for the topic refinement project, there appears to be heterogeneity among the studies and we will consider, a priori, a random effects model for analysis. The reasons for the heterogeneity we noted include varied study population characteristics, varied stratification methods for pretest risk, and varied definitions of the end point acute renal injury or contrast induced nephropathy. However, we will assess heterogeneity for each meta-analysis by visual inspection of forest plots and cumulative meta-analysis. These plots are useful in the initial assessment of statistical heterogeneity. A test for the presence of statistical heterogeneity, for example, Cochran's Q test, as well as a measure for magnitude of heterogeneity, e.g., if the I-squared statistic is greater than the degrees of freedom, we will consider that evidence of significant heterogeneity. Interpretation of Q statistic will consider the limitations of the test that it has low power when the number of studies is small and could detect unimportant heterogeneity when the number of studies is large. In addition, the 95% CI for I^2 statistic should also be provided, whenever possible, to reflect the uncertainty in the estimate. Though a naïve categorization of values for I^2 would not be appropriate for all circumstances, we would tentatively assign adjectives of low, moderate, and high to I^2 values of 25%, 50%, and 75%. When statistical heterogeneity is attributable to one or two "outlier" studies, sensitivity analyses would be conducted by excluding these studies. Sensitivity analysis could be performed for pretest risk stratification methods or groups, varied methods of defining the CIN or acute renal injury and for varied methods (infra versus supra renal) of intra arterial injection of intravenous contrast to investigate the impact on heterogeneity. However, a clear and defensible rationale would be provided for identifying "outlier" studies.[36,38]

We will measure both short-term and long-term outcomes, We will collect short-term outcomes for RCTs defined as outcomes reported within 7 days post-procedure. We will collect long-term outcomes at least 30 days post procedure, and any longer-term final outcome measure reported. For observational studies we will collect only data collected at 2 year followup.

F. Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes – At the completion of this review, two reviewers will independently grade the strength of evidence on key outcomes, including harms of the intervention, renal function measures, renal disease specific outcomes, cardiac outcomes, in-hospital mortality, and image quality. We will use the grading scheme recommended in the Methods Guide.[38] We will consider all domains: study limitations, directness, consistency, precision, reporting bias, dose-response association, plausible confounding that would decrease observed effect, and strength of association (magnitude of effect).[42]

We will classify the evidence pertaining to the key questions into four categories: high grade (high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); moderate grade (moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of effect); low grade (low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the effect estimate); and insufficient grade (evidence is unavailable or insufficient to assess with any confidence).

G. Assessing Applicability – We will consider elements of the PICOTS framework when evaluating the applicability of evidence to answer our Key Questions as recommended in the Methods Guide.[38] We will consider important population characteristics, treatment characteristics, and settings that may cause heterogeneity of treatment effects and limit applicability of the findings.

V. References

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VI. Definition of Terms

All terms have been defined in the text of this protocol.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Table 1: Most recent meta analyses

Meta analysis	Population	Conclusion	Key Question
Kooiman et al 2012{Kooiman, 2012 #27}	Prospective and retrospective studies with patients received only intravenous contrast media	CIN occurred in 6% of patients after contrast enhanced CT. In 1% of all patients undergoing contrast enhanced CT the decline in renal function persisted.	Part of KQ 1
McDonald 2013{McDonald, 2013 #5}	CTs with Patients received intravenous contrast media enhanced CT versus patients had CT without contrast media	Controlled contrast medium–induced nephropathy studies demonstrate a similar incidence of AKI, dialysis, and death between the contrast medium group and control group.	Part of KQ 1
Dai et al 2012{Dai, 2012 #28}	RCTs with and without the prevention strategy of theophylline administration	Theophylline treatment significantly reduced the incidence of contrast-induced AKI and had a modest improvement on kidney function after contrast exposure. However, beneficial effects of theophylline were not observed in patients with high baseline creatinine values (serum creatinine _1.5 mg/dL).	Part of KQ 2
Li et al 2012{Li, 2012 #31}	RCTs with and without the prevention strategy of statin administration	The use of short-term high-dose statin treatment was associated with a significant reduction in risk of CIN. However, the incidence of acute renal failure requiring dialysis was not significant different after the use of statin	Part of KQ 2
Jang et at 2012{Jang, 2012 #29}	RCTs with sodium bicarbonate versus sodium chloride as prevention strategy	The sodium bicarbonate-based hydration is superior to sodium chloride in preventing CI-AKI of patients undergoing exposure to iodinated contrast media.	Part of KQ 2
Sun 2013{Sun, 2013 #30}	RCTs with one arm receive NAC versus other preventive strategy before or after CM administration and varied doses of NAC	A nonsignificant trend towards benefit in patients treated with intravenous NAC. There was evidence of significant heterogeneity in NAC effect across studies.	Part of KQ 2
Moos 2013{Moos, 2013 #26}	Prospective and retrospective Studies with patients received intravenous contrast media for CT	The overall pooled CIN incidence was 4.96%.	Part of KQ 1

CT=computerized tomography; KQ=Key Question; AKI=acute kidney injury; RCT=randomized controlled trial; CIN=contrast induced nephropathy; CI_AKI=contrast induced acute kidney injury; NAC=n-acetyl cysteine

Table 2. Major prevention interventions and comparisons for Key Question 1 and Key Question 2

(These are the important comparisons that are most likely to have sufficient evidence to merit inclusion in a systematic review. Other comparisons may be identified after a more thorough literature search, but they are unlikely to be relevant to modern clinical practice or have enough evidence to merit inclusion in the review.)

Interventions → Comparators ↓	IV Volume expan-sion with NaCL	IV Volume expan-sion with Bicarb	IV Volume expan-sion with NaCL and Bicarb	IV or oral NAC (high dose)	IV or oral NAC (high dose plus bicarb)	IV fluids without pharma-cologic agents	IV fluids with pharma-cologic agents*	IV Fluids matched to urine output	Oral fluids	Discontinuation of metformin or drugs that have adverse effects on kidney function					
										RRT†-HD	RRT†-HF	Oral Statins	ACE inhibitor	ARB	IV Dop-amine
Usual Care (Oral fluids)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Volume expansion with NaCL		√	√												
Volume expansion with Bicarb			√												
NAC (low dose)				√	√										

Bicarb= bicarbonate; NAC = N-acetylcysteine; NaCl = sodium chloride; IV = intravenous; RRT-HD = hemodialysis; RRT-HF=hemofiltration; ACE=angiotensin-converting enzyme; ARB=angiotensin II receptor blockers.

√ = comparison

* pharmacological agents include: calcium antagonists, theophylline, aminophylline, dopamine, fenoldopam mesylate, atrial natriuretic peptide, statins, mannitol, Mesna fluid, allopurinol, furosemide, trimetazidine, anisodamine, probucol, pentoxifline, and benazepril

† RRT is an intervention that may not be included in key questions 1 or 2.

Table 3. Major contrast media and comparisons for Key Question 3 and Key Question 4

(These are the important comparisons that are most likely to have sufficient evidence to merit inclusion in a systematic review. Other comparisons may be identified after a more thorough literature search, but they are unlikely to be relevant to modern clinical practice or have enough evidence to merit inclusion in the review.)

Interventions → Comparators ↓	IOCM	LOCM	IOCM by dose/ volume	LOCM by dose/ volume	IOCM by # doses	LOCM by # doses
Usual care	√	√	√	√	√	√
IOCM		√				
LOCM	√	√				
IOCM by dose/ volume			√	√		
LOCM by dose/ volume				√		
IOCM by # doses					√	√
LOCM by # doses						√

ICOM=iso-osmolar contrast media; LOCM = low-osmolar contrast media; # = number

√ = comparison

Appendix A. Preliminary Search Strategies

PubMed Search:
("Kidney diseases"[mh] OR "Kidney disease"[tiab] OR "kidney diseases"[tiab] OR Nephropathy[tiab] OR "acute kidney injury"[tiab] OR "renal disease"[tiab]) AND ("contrast media"[mh] OR "contrast media"[tiab] OR "contrast medium"[tiab] OR "contrast material"[tiab])

Embase search:
#1.1 AND #1.2
#1.2
'contrast medium' OR 'contrast media' OR 'contrast material'
#1.1
'kidney disease' OR 'kidney diseases' OR nephropathy OR 'acute kidney injury' OR 'renal disease'

Cochrane search:

#1	MeSH descriptor: [Kidney Diseases] explode all trees
#2	"kidney disease":ti,ab,kw (Word variations have been searched)
#3	nephropathy:ti,ab,kw (Word variations have been searched)
#4	"acute kidney injury":ti,ab,kw (Word variations have been searched)
#5	"renal disease":ti,ab,kw (Word variations have been searched)
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Contrast Media] explode all trees
#8	"contrast media":ti,ab,kw (Word variations have been searched)
#9	"contrast material":ti,ab,kw (Word variations have been searched)
#10	#7 or #8 or #9
#11	#6 and #10